REMARKS

Claims 1-4, 6, 9-12, 14, and 23-26 are pending in this application. The instant Supplemental Amendment is supplemental to the Amendment filed October 7, 2005. By virtue of the amendment filed October 7, 2005, claims 1 and 6 were amended without prejudice or disclaimer of any previously claimed subject matter. By virtue of the instant amendment, new claim 27 has been added. Support for new claim 27 can be found at pages 21-22 of the specification. Applicants request entry of the instant Supplemental Amendment subsequent to entry of the Amendment mailed October 7, 2005

Interview Summary

Applicants thank Examiner Lucas and Examiner Housel for extending the courtesy of a telephonic interview on October 27, 2005 regarding the outstanding rejections in the instant application. The following is a list of participants of the Telephonic Interview of October 27, 2005: USPTO participants: James Housel and Jachariah Lucas; Applicants' Morrison & Foerster, LLP representatives: Catherine Polizzi and Debra Glaister; and Applicants' representative: Kenneth Goldman. The pending claims and references cited by the USPTO were discussed. Applicants thank Examiners Housel and Lucas for their helpful comments and suggestions, which are reflected herein.

Rejection Under 35 U.S.C. §112, Second Paragraph

Applicants gratefully acknowledge Examiner Lucas' agreement in the Telephonic Interview that the amendment to claim 1 should obviate the Section 112, second paragraph rejection of claims. Applicants respectfully request withdrawal of this rejection of claims.

Rejection Under 35 U.S.C. §103

Claims 1-4, 6, 9-12, 14, and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beutner *et al.* (1998, *J. Am. Acad. Dermatol.* 38: 230-239 "Beutner"), Bauman *et al.* (1996, *Pediatr. Clin. N. Am.* 48(6): 1385-1401 "Bauman"), and Yamamoto *et al.*

(1994, *Jpn. J. Cancer Res.* 85: 775-779 "Yamamoto"), and further in view of Raz *et al.* (U.S. Patent 6,514,948 "Raz") and Schwartz *et al.* (WO 98/55495 "Schwartz").

Applicants respectfully traverse this rejection and reiterate their arguments presented in the Response filed October 7, 2005.

Claim 1 is directed to a method of delaying development of a lesion associated with papillomavirus infection in a human, by administering an immunostimulatory polynucleotide (ISS) in the absence of a papillomavirus antigen. Claim 9 recites, in part, a method of reducing severity of a lesion associated with papillomavirus infection in a human, by administering an ISS in the absence of a papillomavirus antigen.

Although the core references cited to support this Section 103 rejection of claims (that is, *Beutner, Bauman, Yamamoto,*) were previously found to be insufficient to support a Section 103 rejection of claims (*See* Office Action in this application mailed December 16, 2004, at page 5 [withdrawing this rejection]), the Examiner has relied on these references in the current rejection. In the Office Action in this application mailed December 16, 2004, at page 7, the Examiner alleges that:

(a) Beutner teaches that an IFN-α inducer (imiquimod) is useful to treat papillomavirus infections;

(b) Bauman teaches that administration of IFN-α *per se* is useful to treat papillomavirus infections; and

(c) Yamamoto teaches that ISS induces IFN-α;

and therefore it would be obvious to treat papillomavirus infection with an ISS alone. However, on closer inspection, these three references do not provide the logical underpinning for this rejection.

Beutner relates to treatment of genital warts with imiquimod and has no disclosure of any ISS. Beutner states that it is not known which cytokine(s) or even biological activity(ies) of imiquimod account for imiquimod's therapeutic effect. Imiquimod induces **not just** IFN-α , but

rather a variety of cytokines, including IFN-α, TNF-α, and IL-6. Beutner, at page 237, left column last paragraph states the following:

> In human peripheral blood mononuclear cells, imiquimod induces IFN-α, IL-1 and TNF-α but not IL-2. Human keratinocytes exposed to imiquimod demonstrate an increase in messenger RNA for IL-1, IL-6 and IL-8. Which of these cytokines accounts for the clinical response is not yet known. (Emphasis added).

Further, Beutner at page 237, right column, last paragraph states the following:

> Which one or combination of the potential biological activities of imiquimod accounts for its therapeutic effect on genital warts remains to be defined.

Beutner does not provide any certainty with respect to any single cytokine's effect on genital warts, and does not disclose any ISS. Accordingly, Beutner does not teach or suggest that a drug that induces IFN-α alone is useful to treat papillomavirus infection.

Furthermore, the Press Releases listed as items 17 and18 along with item 36 on the Supplemental Information Disclosure Statement (SIDS) submitted concurrently herewith demonstrate that not all IFN-α inducers have produced adequate efficacy in the treatment of viral infection and not all IFN-α inducing therapies for viral infection have produced accepted results. The Press Release published February 24, 2003 (item 18), is a disclosure regarding the suspension of Eli Lilly and 3M Phase III clinical trials of resiquimod (reported to induce cytokines, including IFN-α , see item 34 on the SIDS submitted concurrently herewith) for the potential treatment of herpes simplex virus (HSV) due to a showing of inadequate efficacy. As stated in the Press Release:

> Eli Lilly and company (NYSE:LLY) and 3M (NYSE:MMM) announced suspension of clinical trials of resiquimod, an investigational compound for the treatment of genital herpes, because preliminary data from recently completed phase III clinical trials suggest the dosing of resiquimod used in the studies will not achieve adequate efficacy.

The Press Release supports that adequate efficacy of a IFN-α inducer in the treatment of viral infection is unpredictable. There is no reasonable expectation provided by Raz, Beutner and Bauman, alone or together, that a cytokine inducer, such as imiquimod, an ISS, and IFN-α would function equivalently in the treatment of viral infection. The combination of Raz with Beutner, Bauman and Yamamoto fails to support a Section 103 rejection.

Bauman relates to recurrent respiratory papillomatosis and discusses IFN-α, along with other therapeutics (but **not** ISS), as adjuvant therapies to surgical excision (that is, as therapies to be used **in conjunction with** surgical excision). See Bauman at page 1393 under the heading "Adjuvant Setting". Bauman, at page 1395, right column, states the following:

> Initiation of α-IFN therapy currently is recommended for patients requiring four or more surgical procedures in 12 months.

Accordingly, Bauman does not teach or suggest that IFN-α alone is useful to treat papillomavirus infection, but rather only shows the use of IFN-α in an adjuvant setting in conjunction with surgical excision.

Yamamoto teaches that certain synthetic oligonucleotides stimulate production of a variety of cytokines, especially IFN-α. –β, and –γ. See Yamamoto, at page 775, left column. Yamamoto does not disclose any viral treatment and shows only *in vitro* results in murine spleen cells. Accordingly, Yamamoto does not teach or suggest that ISS induces any cytokines *in vivo*, including IFN-α.

So, upon close examination of the core references, it is clear that the three points upon which the Examiner bases his rejection do not support this obviousness rejection. Neither Raz nor Schwartz add the requisite disclosure to overcome the deficiencies of the core references.

In contrast to the claimed invention, Raz discloses "pre-priming", or administering ISS prior to exposure to an infectious agent. See Raz col. 1, at lines 45-55. Furthermore, there is no disclosure in Raz of papillomavirus. If Raz teaches a different timing for administration of an ISS

than the claimed invention and does not disclose papillomavirus, one of skill in the art would not be motivated to combine Raz with Beutner, Bauman and Yamamoto. Even if the references were combined, one of skill in the art would not arrive at the claimed invention.

With respect to the Examiner's allegations that all three of Raz, Beutner and Bauman are concerned with ISS molecules (instant Office Action at page 5), Applicants point out that Raz discloses ISS; Beutner discloses the use of imiquimod, known to induce a variety of cytokines; and Bauman discloses use of IFN-α, among other adjuvants, in addition to surgical excision. The Examiner states at page 5 of the Office Action that "the common purposes and functions of the adjuvants[1] used in these references [Raz, Beutner, Bauman] indicate that they are functional equivalents". As discussed in the Amendment mailed October 7, 2005 and the October 27, 2005 Telephonic Interview, the Examiner's allegation that all three are functional equivalents is not supported by the references themselves.

Schwartz does not cure the deficiencies of Beutner, Bauman and Yamamoto. Schwartz does not teach or suggest delaying development of a lesion associated with papillomavirus infection or reducing severity of a lesion associated with papillomavirus infection. The Examiner cites page 4 and page 29 of Schwartz for support. Page 4 of Schwartz refers to ISS present in an *antigen-encoding* plasmid that prompted the production of IFN-α and –β. Page 29 of Schwartz refers to specific ISS as stimulators of secretion of IL-12, IFN-γ and IL-6. Contrary to the Examiner's allegations, Schwartz does not teach or suggest that administration of an ISS containing polynucleotide *without antigen* results in production of IFN-α. The combination of Schwartz with Beutner, Bauman and Yamamoto fails to support a Section 103 rejection.

In view of the above, Applicants submit that there is no motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Even if the references were properly combined, which Applicants don't concede, the combination does not teach or suggest the claimed

[1] Applicants note that the claims recite that the papillomavirus antigen is not administered in conjunction with administration of the composition which comprises a polynucleotide comprising an ISS.

invention, and the combination does not provide a reasonable expectation of successfully arriving at the claimed invention. In view of the above, Applicants request reconsideration and withdrawal of the rejections of claims under Section 103.

CONCLUSION

Applicants believe that the pending claims are in shape for allowance. If it is determined that a further telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 17, 2005

Respectfully submitted,

By _____

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